



A Global overview on WHO Perspective of Neglected Tropical Diseases

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Abstract

WHO has identified 20 neglected diseases in total, which are the primary cause of illness worldwide, prevalent mostly in the tropical areas of the world. The majority of these diseases are found in poverty-stricken rural areas, which affects almost 700 million people worldwide, or 10% of the world's population. The major goal of this article is to raise awareness of these diseases among all people, as they have all been ignored for decades due to the escalating severity of other illnesses including HIV/AIDS, tuberculosis, and malaria. A person's location, living conditions, and marginalisation as well as poverty are all factors that contribute to their suffering, incapacity, and eventual mortality. Most of the impoverished people in these disease-affected areas don't have access to the same level of medical care as those in industrialised places do. Despite the pharmaceutical industry's efforts to make things better, NTD control remains incredibly weak and difficult. A significant contributing factor is the lack of accessible, reliable, and efficient drugs. In this article, the aetiology, management, and prevention of a few neglected diseases are discussed.

Introduction

According to the World Health Organization, neglected tropical diseases are a group of diversified diseases that are widespread in poverty-stricken areas in developing countries that mostly affect women and children. It could be due to bacteria, viruses or parasitic infections. The cause and spread of these diseases are often related to the environment and living conditions of these people (1).

The 20 neglected diseases mentioned by WHO include

1. Buruli ulcer
2. Chagas disease
3. Dengue and severe dengue
4. Dracunculiasis
5. Echinococcosis
6. Trematodiasis
7. Human African Trypanosomiasis
8. Leishmaniasis
9. Leprosy

10. Lymphatic filariasis
11. Mycetoma
12. Onchocerciasis
13. Rabies
14. Scabies
15. Schistosomiasis
16. Soil-transmitted helminthiasis
17. Snakebite envenoming
18. Cysticercosis
19. Trachoma, and
20. Yaws and other endemic treponematoses

These diseases often worsen the living conditions of people and affect their mental growth along with negative impacts on their cognitive growth. NTDs are usually fatal to humans or degrade their living to a great extent. The diseases are also known to affect the productivity and earnings of these people in their workplace. People are often caught in a vicious cycle of poverty and illness which is extremely tough to get out of. The disease spreads to the entire family gradually when one member catches the infection leading to a concatenated cycle. The disease eats up the entire family leading to unwanted circumstances and is a source of never-ending extreme suffering (2).

A few of the Neglected Tropical Diseases are explained in short and a few in detail below

Dracunculiasis

Commonly known as Guinea Worm Disease (GWD) is caused by the parasite known as *Dracunculus medinensis*. The disease occurs by drinking contaminated water containing guinea pig larvae. It infects the lower limbs of a person and causes an intense blister which can be painful (3).

Mycetoma

This disease is caused by certain water and soil bacteria which usually affect the foot but can be found anywhere on the body. It starts as a painless lump under the skin and proceeds to develop with time. It grows in size considerably over time leading to the formation of sores and then leading to the deformation of the limb (4).

Lymphatic Filariasis

It is a disease caused by microscopic thread-like worms that usually don't show symptoms in humans in the early stages but long-term infection of the lymphatic system may lead to swelling of legs, arms, genitalia and other parts of the body. It also increases the risk of further bacterial infections and leads to the thickening of the skin (5).

Leprosy

The infection of *Mycobacterium leprae* causes leprosy. It is a contagious disease that affects the skin, mucous membrane and peripheral nerves which causes a very light-coloured, red skin patch along with a reduced sensation of the nerves. It is also known as Hansen's disease (6).

Leishmaniasis

It is a disease caused due to the bite of sandflies that transmit the leishmania parasite. It affects the skin and internal organs and mostly occurs in tropical and subtropical areas (7).

Soil-Transmitted Helminthiasis

One of the most common infections worldwide refers to intestinal worms that infect the human population and are transmitted by soil affecting poor people. There are different types of worms causing the infection which include Roundworm (*Ascaris lumbricoides*), Whipworm (*Trichuris trichiura*), Hookworm (*Ancylostoma duodenale* and *Necator americanus*), Threadworm (*Strongyloides stercoralis*) (8).

Nearly 121 million people are affected by *Ascaris* and 604-795 million people get affected by whipworm. 576-740 million people have been infected by hookworm. More than 1.5 billion people, of the total world's population, are infected with soil-transmitted helminth infections worldwide. It mainly infects those who live in tropical and subtropical regions with poor hygienic conditions (8).

STH can be transmitted via the worm eggs, which are present in contaminated water, undercooked and unpeeled vegetables and thus by the human intake of these products. The larvae of the helminths can come in contact by walking barefoot on grounds containing the larvae. It can be transmitted when children eat contaminated soil while playing in the park. The pathophysiology of STH includes direct damage that can be done by the helminths through the destruction of intestinal organs by blocking

certain ducts which can lead to anemia, inflammation, and mucosal damage depending upon the organism. Indirect damage is the response of the immune system of the host against the helminths that could lead to a hypersensitivity reaction. Irreversible loss of tissue can occur with a prolonged infection (9).

The clinical presentation of light soil-transmitted helminth infection shows no symptoms but heavy soil-transmitted helminth infection is abdominal pain, nausea, diarrhea, general malaise and weakness, malnutrition, blood and protein loss, and impaired physical and cognitive growth and development (10).

To diagnose the STH condition some of the diagnostic tests include Microscopical Diagnosis i.e. detection of helminth eggs in stool samples. Antibody Test i.e. for strongyloidiasis, development of antibody ELISA diagnostic tests, by using larval antigen and recombinant protein. Antigen Detection i.e. for certain species of helminths the presence of antigen can be found in faeces (eg hookworm). Molecular Diagnosis is a type of PCR diagnosis that has been able to detect the number of helminth eggs (11).

Non-Pharmacological Treatment for the prevention of STH includes sanitary disposal of the human excreta, drinking filtered water, clean hygiene practices, and wearing protective footwear in those areas with contamination. Washing fruits and vegetables well, as well as not eating undercooked food. Deworming pets is very necessary. Lastly, we need to follow the WASH principles - Water, Sanitation and Hygiene (12).

The Pharmacological Treatment of STH includes the following medication

MEBENDAZOLE is used as a drug of choice for whipworm, pinworm, roundworm, and hookworm. Adverse drug reactions include nausea, vomiting, diarrhea, and abdominal pain. It is contraindicated in pregnancy and children below 2 years. The dosing of mebendazole is 100mg per day.

ALBENDAZOLE is a broad-spectrum anthelmintic drug whose dosing is 400mg. The adverse drug reaction includes mild epigastric pain, diarrhea, headache, nausea, and dizziness. It is contraindicated in pregnant women and dose reduction should be done in hepatic or renal disease.

PYRANTEL PAMOATE is used in combination with mebendazole. The adverse drug reaction includes nausea, vomiting and diarrhea. The dose is around 11mg/kg.

DIETHYL CARBAMAZEPINE has a selective effect on microfilariae. The dosing is about 2mg/kg TDS and the adverse drug reactions are nausea, loss of appetite, weakness and dizziness (13).

Rabies

Rhabdovirus disease or rabies is a nervous system disorder in mammals caused by the rhabdovirus and transmitted through the bite of a rabid animal. It is usually characterized by increased salivation, and abnormal behavior, and eventually leads to death when left untreated. Rabies is a contagious and fatal viral disease of dogs and other mammals which is transmitted through saliva to humans and causes madness and convulsions (14).

In over 150 countries, rabies leads to more than 59000 deaths every year, with 95% of cases occurring in Africa and Asia. 99% of rabies cases are dog-mediated and the burden of the disease is disproportionately carried by rural poor populations. Approximately half of the cases are of children up to the age of 15 years (14).

The disease is transmitted by the bite of rabid animals which have infectious viruses within their saliva. The virus enters the body through transdermal inoculation (wounds) or direct contact of infectious material with mucous membranes or skin lesions. The virus can not penetrate intact skin. After the entry of the virus, it binds to the cell receptors and starts replicating or infecting nerve cells. The virus then travels via retrograde axoplasmic transport mechanisms to CNS. Once it reaches CNS, rapid virus replication takes place, which causes a pathologic effect on nerve cell pathology. The virus then moves through CNS via anterograde axoplasmic flow in the peripheral nerve and leads to infection of some adjacent non-nervous tissues, like secretory tissues of salivary glands (15,16).

The incubation period ranges between 2-3 months based on the location of the infection and the strain of the virus. Due to its neurotropism, known Lyssaviruses can cause severe neurological symptoms as a result of acute encephalitis. The clinical symptoms in humans and animals are very similar (16).

The initial symptoms are non-specific and can be similar to other infections. The first specific symptom is neuropathic pain or an itchy or prickling sensation at the site of the bite. Other symptoms include cerebral dysfunction, anxiety, confusion, agitation, delirium, abnormal behaviour, hallucinations, and insomnia (16) .

Animals usually stop eating and drinking, become lethargic, and may show symptoms of fever, vomiting, and anorexia. Due to the rapid progression of the disease, the animal becomes vicious. Clinical signs include cerebral and cranial nerve dysfunction, ataxia, weakness, paralysis, seizures, difficulty breathing, difficulty swallowing, excessive salivation and abnormal movement (16).

The rabies infection must be confirmed by a number of tests on serum, saliva, spinal fluid, and skin biopsies. There are two main types of tests used in rabies suspects : fluorescent antibody test and

inoculation test. The fluorescent test is based on antigen detection, it is the gold standard test for rabies diagnosis. It detects specific aggregates of rabies virus antigen smears from brain tissue which are prepared and treated with antirabies serum or globulin labeled with fluorescein isothiocyanate (FITC) using a reflected light fluorescence microscope (17).

If the person has a bite or scratch from a rabid animal, the individual should immediately wash bites and scratches for 15 minutes with soapy water, povidone-iodine, or detergent. This will minimize the number of viral particles. After exposure, before the symptoms begin, a series of shots (rabies vaccine) is given to the patient, which can treat the potential rabies infection (17).

HDCV or PCECV vaccines are administered intramuscularly to the patient. The first four doses (1ml each) are given as soon as possible after exposure, and the subsequent doses are administered after 3, 7, and 14 days. In adults, the vaccination should always be administered intramuscularly in the deltoid area (arm) and for children, the anterolateral aspect of the thigh is acceptable. Rabies vaccine injections are never performed in the gluteal area since it results in a lower level of neutralizing antibodies (18).

To reduce the risk of rabies, individuals should follow a few safety rules, Keep your pets' vaccinations up to date by vaccinating cats, dogs, ferrets, and other farm or domestic animals, and protect small pets from wild animals, while at home, pet owners should confine their pets safely or supervise their pets (18).

Cysticercosis

This extremely rare disease with fewer than 5000 cases per year worldwide is known to be caused by larval cysts/eggs of the tapeworm *Taenia solium*. Brain and muscles are most commonly infected along with other body tissues which often leads to early onset of adult seizures in most low-income countries. In some places, it is also known as Neurocysticercosis or Solitary Cysticercus Granuloma (19),.

Although the disease is found to exist all over the world, it is most likely to affect Latin Americans, Asians and Africans due to their poor living conditions where 10 to 20 percent of individuals have evidence of the disease. It can affect all age groups but is most likely to be seen in the age group of 10 to 40 years. The disease is seen to develop when a human ingests the eggs of the tapeworm by either consuming water/food infected by the tapeworm eggs or eating products that have been irrigated by the contaminated water or living in highly unhygienic conditions. When the eggs enter the human body, they hatch to produce larvae which enter the bloodstream and are carried to one or more parts

of the body along with the blood over a period of three to eight weeks and then form cysts in those places. Thus, the disease can develop in any part of the body but is most likely to affect the brain, eyes and subcutaneous tissues. Cysts are developed by the parasite as it aids them to invade the host's immune system and survive there for years. Eventually, with time the cysts degenerate and start to die, that is exactly when the immune system of the host activates and acts by producing inflammation of the tissues surrounding the cysts. The response of the immune system, thus, produces the symptoms of the infection (19,20)

The symptoms of the disease differ based on the location of the cysts in the body and the response of the host's immune system to the cysts. Seizures, headaches, nausea, arachnoiditis, altered brain responses and altered vision are usually seen in the conditions when cysts are accumulated in the nervous system. Retinitis, uveitis, loss of vision, limited eye movement are the symptoms when cysts are in the eye. If the cysts are developed outside of the nervous system, the symptoms are not seen distinctively and the person is usually asymptomatic. Though, small hard lumps can be seen under the skin which disappears over time (20).

Cysticercosis can be suspected in people by the episodes of seizures or by the symptoms of increased intracranial pressure. The diagnosis is done based on the characteristic sign and symptoms in an individual with reference to detailed patient history, neuroimaging findings like MRI or CT scanning and exposure to certain risk factors. Blood workup and biopsy can also be done in instances of neurocysticercosis (cysts in the brain) (20).

Once, the diagnosis is confirmed, the treatment is thus, then based on the location of the cysts in an individual and is usually individualized for each patient. In case of the presence of cysts outside the nervous system, no treatment is required as such because the disease is benign. But, if the cysts are present in the nervous system, a combination of antiparasitic drugs, antiepileptic drugs and corticosteroids are given. Surgery can also be considered in extreme cases (21).

Antiparasitics are recommended to kill the parasites in the body. FDA approved Albendazole for the treatment of the disease in 1996. It is often given in combination with praziquantel. Antiparasitic drugs are contraindicated in people with high intracranial pressure or if they have ophthalmic cysticercosis (21).

Chagas Disease

Chagas disease, also known as American trypanosomiasis, is an inflammatory disease that is transmitted by the parasite *Trypanosoma cruzi*. This parasite is found in the feces of triatomine bugs. This disease is commonly found in the areas of South America, Central America and Mexico (22).

This disease is caused by blood infection due to the *Trypanosoma cruzi*. Patients who are exposed to Chagas disease are from the feces or urine of the infected triatomine bug. It is also known as ‘kissing bugs’ as they bite at night during our sleep and leave bite marks on or around the face region. This kissing bug feeds on humans and animals (22).

It is endemic in 21 countries in America and has affected 6 million people approximately. Annual Incidence of 30,000 new cases, 12,000 deaths per year and 8,600 newborns get affected during the gestation period (23).

Chagas disease generally spreads through the bite of the triatomine bug from an infected person to another. This triatomine bug when bites a human it deposits its feces near the wound or bite which contains metacyclic trypomastigotes. These parasites when penetrating the wound through the mucous membranes of the skin, they invade the macrophages and convert into amastigotes. These amastigotes multiply in binary fission and convert into trypomastigotes. Trypomastigotes enter the bloodstream and infect other cells or tissues. Reticuloendothelial system, myocardium, muscles and nervous system are most commonly affected (24).

Symptoms of Chagas disease are very sudden, acute or can be chronic. It occurs in two phases i.e., acute phase and chronic phase. Acute phase includes swelling at the site of infection, fever, fatigue, rash, headache, swollen glands, eyelid swelling, body aches, nausea, diarrhea or vomiting, loss of appetite, enlargement of liver or spleen. Chronic phase includes irregular heartbeat, heart failure, difficulty in swallowing because of the enlarged esophagus, stomach pain or constipation because of enlarged colon, sudden cardiac arrest (25).

This disease can occur due to living in poor areas of Central America, Mexico and South America or living in areas where there are manifestations of triatomine bugs or through blood transfusion or organ transplant from an infected person(26).

Diagnostic tests such as microscopic examination, blood testing or antibody testing helps us in identifying the particular disease.

Benznidazole and nifurtimox are used to kill the parasites. Both medications are effective against the Chagas disease if they are given at the early onset also including the congenital transmission. The efficacy of the drug decreases as the disease progresses for a longer period. These medications are also indicated in the early chronic phase or for the patients in which the infection is reactivated and also includes girls or women before and after pregnancy to prevent congenital spread from mother to baby.

People who are infected but don't show any symptoms should be medicated with antiparasitic drugs as they can help to prevent the disease progression. Benznidazole and nifurtimox should not be given to pregnant women or to kidney or liver failure patients. Nifurtimox is contraindicated in patients with neurological or psychiatric disorders. Specific treatment is required for cardiac, digestive or neurological manifestations.

Some precautions can be taken such as spraying of areas and surroundings with insecticides, avoid sleeping outdoors or in-poor built houses that are made from mud, sleep under the bed net which is treated with insecticides, test the donated blood or organ before undergoing any transfusion or transplanting any organ.

Dengue Fever

The word dengue is derived from the word 'denga' meaning fever with hemorrhage. Dengue fever is a mosquito-borne tropical disease caused when an infected mosquito with dengue virus bites a human. It can spread from one person to another through mosquitoes. The mosquito responsible for spreading the dengue virus is *Aedes aegypti*. Mosquitoes take up the virus when they bite the person infected with the dengue parasite and thus become carriers of the parasite and potential danger to the healthy human (29).

There are four types of dengue viruses designated as DENV-1, DENV-2, DENV-3, and DENV-4. These viruses infect endothelial cells, blood monocytes and lymphocytes. The infection with one type of dengue virus induces immunity for that type of virus only and does not provide cross-protective immunity to the other remaining serotypes. It is most common in children under the age of 15 (30).

Dengue fever can be classified into two main types: The first is dengue fever or break-bone fever which is called so due to myalgia that affects muscles and joints along with uncomplicated back pain. The second is dengue hemorrhagic fever (DHF), unlikely to happen, it is a severe and potentially fatal form of acute febrile illness-causing intestinal and cutaneous hemorrhages due to thrombocytopenia,

hypovolemic shock, neurological disturbance and hemoconcentration. Dengue virus infection is either symptomatic or asymptomatic depending on the individual's immunity (31).

Annually around 50 million dengue infections are recorded. Its incidence has increased 30-fold in the last 50 years with an increase in new countries. In India, the incidence of infection since 2010 has increased to 15 per million people annually in different states. 10000 infections and 200-400 deaths occur every year due to dengue infection. In 2017 the last epidemic was recorded in which 18,401 infections and 325 deaths occurred.

When the mosquito, *Aedes aegypti*, bites a human, the virus penetrates into the skin. Once the virus has penetrated, it infects and starts replicating inside the Langerhans cell. The Langerhans cells release interferons to limit the spread of infection. Also, the infected Langerhans cells go to the lymphatic system to activate the immune system & later on go to blood circulation which results in viremia. This leads to immune system activation (i.e lymphocytes count increase). But there is a subsequent decrease in neutrophils and white blood cells that leads to the release of pyrogen which causes fever in turn(32).

In mild cases of dengue fever, many people, especially children and teens may not show any signs and symptoms. Generally, the incubation period is 4-7 days when symptoms are observed. A high fever of, generally, 104°F is observed in dengue. Its symptoms usually include severe stomach pain, nausea, persistent vomiting, rashes, aches and pains, eye pain (typically behind the eyes), muscle, joint, or bone pain, bleeding from gum or nose, blood in urine, stool or vomit.

The nucleic acid amplification test (NAAT) is a preferred test used for laboratory diagnosis of dengue for patients suspected of dengue virus. Serological tests such as IgM testing & IgG testing are also done to confirm the diagnosis.

The main aim of the treatment is to manage the symptoms and keep the infection from becoming more severe. An over-the-counter drug such as paracetamol or crocin can help treat pain and fever. Patients need to drink more and more water to stay hydrated. In many severe cases, patients may need emergency treatment such as intravenous fluids (saline) for hydration and supportive care in the hospital. Sometimes, they may even require a blood transfusion due to blood loss. NSAIDs such as aspirin and ibuprofen are to be avoided as they can increase the risk of bleeding (28).

There are no vaccines till date that can prevent dengue fever. One should avoid the collection of stagnant water which provides the mosquitoes with a breeding ground. To avoid mosquito bites when travelling to high-risk areas such as Northern Australia, Central and South America, the Caribbean,

Tropical Asia, including Bangladesh, Indonesia, and parts of China, one should wear full sleeves cloth, use mosquito nets, apply mosquito repellents and follow other safety practices.

Conclusion

Neglected tropical diseases, the group of parasitic and bacterial infections are one of the major concerns in the rural and rustic areas. These diseases not only remain in the region specified but have outgrown various other nations, irrespective of the endemic and non-endemic regions. The people living in poverty and unhygienic conditions, devoid of basic amenities and medical assistance are the prime prey of these diseases. Though extremely severe and cynical to cure, they can be controlled and eradicated with effective administration of certain measures in the mass. The cure to eradicate these diseases is still an issue of concern but the treatment, diagnostic characteristics are improving which is one more step towards attaining the cure of these diseases.

Certain interventions are recommended by WHO to combat NTDs

Preventive chemotherapy and transmission control (PCT) It ensures that safe and effective drugs are available for everyone.

Innovative and intensified disease management (IDM) The use of this measure is to eliminate NTDs as public health problems by treating them within the primary healthcare level.

Veterinary public health services plays an important role as many of these diseases are zoonotic and henceforth spread from animals, which must be taken care off to prevent their spread.

Vector biology and the board, Vector the executives centers around compelling strategies for focusing on mosquitoes, flies, ticks, bugs and different vectors that send microbes. Safe water, disinfection and cleanliness.

Admittance to safe water, sufficient sterilization and cleanliness is a critical mediation in the new WHO draft guide. It is basic in the anticipation and arrangement of care for all NTDs.

The WHO approximates that more than one 1 billion people i.e around one-sixth of world's population suffers from at least one Neglected Disease. These diseases can lead to poverty cycle across the world by diminishing quality of life and opportunity to succeed as these diseases rarely lead to death, but can cause significant disability that persist for lifetime, including fatigue, blindness, and disfigurement. Thus, we should bring to an end of neglecting the Neglected Diseases and should promote the global

effort to eliminate, control, prevent and if possible eradicate these diseases by continuous research and development.

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